REMARKS

Claims 1 and 3-17 are pending. Claim 2 has been withdrawn and Claim 15 has been amended. No new matter has been added by way of this amendment, support for which can be found in paragraph 7 of the application, for example. Reconsideration of the present case is respectfully requested.

The pending claims are definite

Claims 7 and 8 are rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite in the recitation of the term "0%" with reference to concentrations of solvent and gelling agent. The Examiner alleged that the criticality of the solvent and gelling agent is unclear because they are claimed at a "0%" concentration.

Applicant respectfully disagrees. Claim 7 recites a composition comprising *about 0% to about 99.8%* of a solvent, and Claim 8 recites a composition comprising *about 0% to about 50%* of a gelling agent. Claim 7 signifies to those with skill in the art that the composition can be without solvent, or comprise up to 99.8% of a solvent. Likewise, Claim 8 signifies to a skilled artisan that the composition can be without a gelling agent or comprise up to 50% of a gelling agent. These claimed ranges are analogous to reciting "up to" 99.8% of a solvent, or "up to" 50% of a gelling agent. The term "up to" has been construed as definite and to include zero as a lower limit. *See, In re Mochel,* 470 F.2d 638, 176 U.S.P.Q. 194 (C.C.P.A. 1974), and M.P.E.P. §2173.05(c)II. These claimed ranges are also similar to reciting "not more than" 99.8% of a solvent, or "not more than" 50% of a gelling agent. Like the term "up to", the term "not more than" has also been construed as definite and to include zero as a lower limit. *See, Ex parte Khusid*, 174 U.S.P.Q. 59 (Bd. App. 1971) and M.P.E.P. §2173.05(c)II.

With respect to the criticality of the gelling agent or solvent, Applicant respectfully submits that in certain embodiments it may be desirable to have a gelling agent and/or solvent present in the composition, and in other embodiments it may not. Support for compositions containing between about 0% to about 99.8% of solvent or about 0% to about 50% of gelling

agent can be found in the published application at paragraphs [0012] and [0031], for example. It is well established that an Applicant is permitted to claim alternative embodiments of their invention. For all of the reasons provided above, Applicant respectfully requests withdrawal of this rejection.

The pending claims are non-obvious

Claims 1 and 3-17 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Allen (U.S. Patent No. 4,895,727) in view of Hellstrand (WO 97/42968), and in further view of knowledge in the art.[1] While acknowledging that the prior art fails to disclose the recited concentrations of a permeation enhancing agent, the Examiner stated that the permeation enhancing properties of histamine were inherent and that it would have been a matter of routine experimentation to discover the optimum or workable concentrations in light of references that teach histamine as a vasodilator. Applicant respectfully disagrees.

To establish a *prima facie* case of obviousness, a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicant submits that the prior art fails to teach or suggest all of the claimed elements of the claims. Specifically, all of the pending claims recite a composition having a permeation enhancing agent that comprises *about 0.001% to about 25% weight/volume* of the total composition, wherein the permeation enhancing agent is selected from histamine, histamine dihydrochloride, histamine phosphate, a pharmaceutically acceptable salt thereof, and other histamine agonists. While Applicant agrees with the Examiner that the cited prior art fails to teach a composition comprising *about .001% to about 25% weight/volume* of a permeation

[1] It is noted that the Examiner characterized Claims 12-17 as methods of manufacturing. This is incorrect. Claims 12-14 are directed to methods of treatment, and Claims 15-17 recite methods of manufacturing.

enhancing agent selected from histamine or histamine-related compounds, Applicant respectfully disagrees that the prior art teaches the claimed invention. Specifically, these claimed concentrations of histamine and histamine-related compounds are not taught, suggested, or inherently present in the prior art.

Applicant further disagrees with the Examiner that it would have been a matter of routine experimentation to discover these optimum concentrations of histamine. It is well established that before optimum ranges or values of a particular variable are characterized as a result of routine experimentation, the variable must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result. *See* M.P.E.P §2144.05(II)(B) citing *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (C.C.P.A. 1977). In *In re Antonie*, the applicant had discovered an optimum ratio of tank volume to contactor area (0.12 gal./sq ft) which maximized treatment capacity of a wastewater treatment device. While the prior art disclosed tank volume and contactor area, the C.C.P.A. allowed the claims because the prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio. In other words, the optimized ratio was not recognized in the art to be a result-effective variable.

Similar to the facts of *In re Antonie*, Applicant was the first to discover that histamine and histamine-related compounds facilitate the permeation of pharmaceutical and therapeutic agents into a subject. Specifically, Applicant discovered that a composition comprising histamine, or a histamine-related compound, having about 0.001% to about 25% weight/volume of the total composition, has the novel and unexpected property of enhancing the transmucosal or transdermal delivery of a drug or vaccine. *See e.g.*, Published Application, paragraph [0009]. This range of concentrations and the effect are not obvious in light of the prior art, nor could it be obtained through routine experimentation, because the prior art failed to even recognize the permeation enhancing property of histamine, as explained below.

As the Examiner readily acknowledges, both of the cited prior art references, Allen and Hellstrand, fail to teach any permeation enhancing property of histamine. Allen's discussion of histamine dihydrochloride is limited to its use as a "counter-irritant" useful in relieving inflammation. *See* U.S. Patent No. 4,895,727, col. 6, lines 5-12. In fact, Allen focuses

extensively on the penetration enhancement properties of zinc-containing compounds, with no suggestion that histamine has similar effects. *See id.* at col. 2, lines 14-45. Histamine is mentioned solely as one of the pharmaceutically active ingredients whose delivery can be enhanced by use of zinc-containing compounds. There is no support anywhere in the reference for the conclusion that histamine has permeation enhancing properties. Similarly, Hellstrand's discussion of histamine and histamine-related compounds is directed to protecting Natural Killer (NK) cells from the harmful effects of monocytes by achieving stabilized levels of histamine in a treated subject. There is no teaching or suggestion of the permeation enhancing effects of histamine. *See* WO 97/42968, page 1, lines 1-15, and page 3, line 32- page 4, line 5.

It is also important to note that contrary to the Examiner's position, the vasodilating properties of histamine do not necessarily signify that this compound increases skin or mucous membrane permeability. While vasodilation increases the permeability of the vascular system, a skilled artisan would not presume that transport of pharmaceutically active compositions into the body would be enhanced. Nor is there any suggestion in the cited art that this is the case. The pharmaceutical must first permeate the skin or mucous membrane before permeating the vascular system. The permeability of blood vessels and skin/mucous membranes are entirely distinct. Accordingly, the prior art is silent as to the usefulness of histamine and histamine-containing compounds as permeation enhancement agents.

As the prior art did not recognize the permeation enhancing effect of histamine, histamine dihydrochloride, histamine phosphate, a pharmaceutically acceptable salt thereof, and other histamine agonists, there would not have been any motivation to determine, or optimize, the concentration of histamine necessary to achieve this effect. Asserting that the recited concentrations of histamine compounds could have been determined by routine experimentation assumes that the permeation enhancement property of histamine compounds was known in the art. As discussed in detail above, the permeation enhancing effects of histamine were not known prior to Applicant's discovery.

For all of the above reasons, Applicant respectfully requests withdrawal of all rejections under 35 U.S.C. § 103, and allowance of the pending application.

CONCLUSION

Applicant has endeavored to address all issues raised in the Official Action. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 8/3/03

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